Analysis COVID-19

Short and long term health effects of COVID-19

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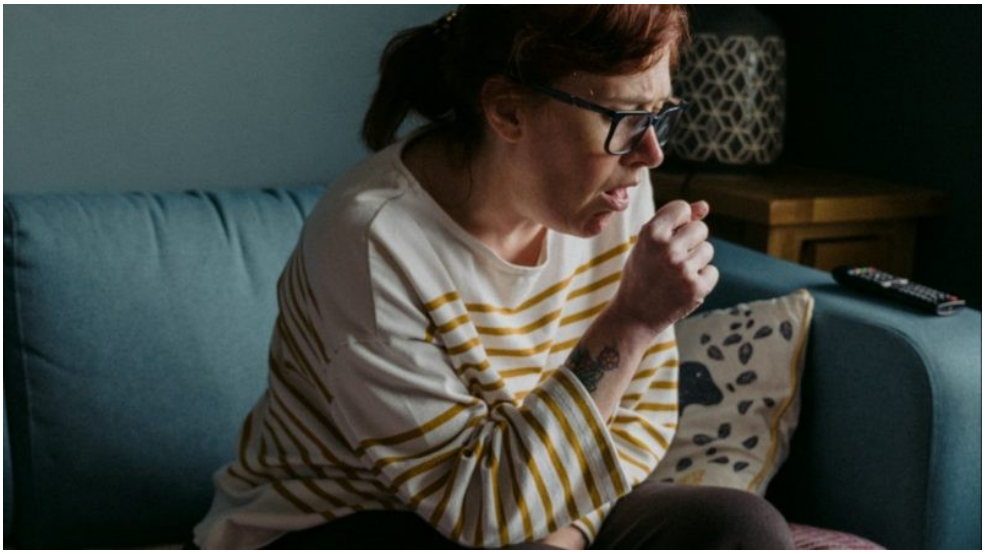

- **There is emerging evidence that COVID-19 affects many systems of the body, with patients reporting a wide range of symptoms.**
- **'Long-haulers' are patients who experience ongoing COVID-19 symptoms for several months after infection. These include fatigue, difficulties in thinking, shortness of breath, chest pain, irregular or abnormal heart rhythm, and joint pain.**
- **Patient-led initiatives, such as the Patient-Led Research**

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effects of 'long COVID'.

- **There is emerging evidence on the long-term health effects of COVID-19. These include long-term respiratory complications, thrombosis, heart failure, kidney injury, fatigue, joint and muscle pain, and metabolic abnormalities.**
- **Long-term cohort studies are needed to better understand long-term disease consequences in COVID-19 patients**.
- **UK-based initiatives, such as the post-hospitalisation COVID-19 (PHOSP-COVID) study and the Research and Innovation for post-COVID-19 Rehabilitation (RICOVR), are currently investigating the long-term effects of COVID-19 and its rehabilitation.**
- **This is part of our rapid response content on COVID-19. The article will be updated as the research progresses. You can view all our reporting on this topic under COVID-19.**

Research on the clinical manifestations of SARS-CoV-2 infection is still ongoing. Over the course of the pandemic it has emerged that SARS-CoV-2 is not only a respiratory virus, but is able to affect many other organs, such as the heart, brain and kidneys. This article summarises the current understanding of acute and long-term COVID-19 symptoms, and the increasing evidence on the long-term effects of COVID-19 on different systems.

COVID-19 symptoms: what are they?

As described on the NHS website, the main symptoms of SARS-CoV-2 infection are: 1) a high temperature, 2) a new, continuous cough, and 3) a loss or change of smell or taste. However, there is emerging evidence supporting a more complex range of clinical features of SARS-CoV-2 infection. Guidance from Public Health England describes the following:

- **more common symptoms**, such as fever; cough; shortness of breath; fatigue; loss of appetite, smell or taste
- **non-specific symptoms**, such as muscle pain, sore throat, headache, nasal congestion, diarrhoea, nausea and vomiting
- **atypical symptoms**, such as delirium and reduced mobility. They manifest in older patients or those who have a weaker immune

A COVID Symptom Tracker app developed by King's College London, Guy's and St Thomas' NHS Foundation Trust, their NIHR Biomedical Research Centre and the healthcare start-up ZOE is currently monitoring 4 million users across the UK, the US and Sweden. By analysing a subset of 1653 app users in the UK and US with confirmed COVID-19, the COVID Symptom Study recently identified six clusters of COVID-19 symptoms. Researchers behind the app suggested that the following symptom clusters could be used as a potential clinical prediction tool:

1. A **'flu-like' cluster with no fever**. Characterised by headache, loss of smell, muscle pain, cough, sore throat, chest pain.
2. A **'flu-like' cluster with fever**. Characterised by headache, loss of smell, cough, sore throat, hoarseness, fever, loss of appetite.
3. A '**gastrointestinal' cluster**. Characterised by headache, loss of smell, loss of appetite, diarrhoea, sore throat, chest pain, no cough.
4. A **'severe level one' cluster**. Characterised by headache, loss of smell, cough, fever, hoarseness, chest pain, fatigue.
5. A '**severe level two' cluster**. Characterised by headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain.
6. A **'severe level three' cluster**. Characterised by headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain, shortness of breath, diarrhoea, abdominal pain.

Moreover, by analysing a subset of 336,847 UK users, the COVID Symptom study identified skin rash as a new COVID-19 symptom. On 20 August, the Department of Health and Social Care announced £2 million funding to support the COVID Symptom Study throughout the winter.

COVID-19 long-haulers

The term 'COVID-19 long-haulers' is used to indicate COVID-19 patients who experience ongoing symptoms and complications several months after SARS-CoV-2 infection. This phenomenon is also known as 'long COVID'. The reported symptoms include fatigue, headache, difficulties in thinking, insomnia, vertigo, shortness of breath, chest pain, cough, skin rash, irregular or abnormal heart rhythm, hypertension, and joint pain.

symptoms last?

It is still unclear how many people are affected by long COVID symptoms, or how long they last. Importantly, long-term consequences of SARS-CoV-2 infection can be experienced by the entire range of COVID-19 patients, from those who show no common symptoms of COVID-19 to severe cases. Given that some of these symptoms emerge late, sometimes people experiencing them no longer test positive for the virus.

An Italian study of 143 hospitalised patients who had recovered from COVID-19 reported that 87.4% of them experienced at least one COVID-19-related symptom 2 months after symptom onset. A US-based study on 292 mild COVID-19 cases reported that 35% of them didn't fully recover after 2 weeks following symptom onset. Data collected by the COVID Symptom Study indicate that 10% of people (often classified as 'mild' COVID-19 cases) experience prolonged symptoms after 3 weeks or more. Anecdotal reports suggest that long COVID symptoms can last more than 4 months.

It is also unclear for how long long-haulers are still infectious. A single study (not peer-reviewed) reported on a case study of a patient able to shed SARS-CoV-2 for 49 days.

Why does it happen?

The reasons behind long COVID are still unclear and immunology studies on the subject are needed. Scientists have hypothesised three possible scenarios underlying long COVID symptoms: 1) a reservoir of virus, hiding and reactivating; 2) virus particles not eliminated by the body activating an immune response; and 3) an autoimmune disease generated by the infection.

Patient-led research initiatives to study and support long-haulers

In the past few months there have been many anecdotal reports of long COVID symptoms, including from infectious disease experts experiencing these symptoms themselves. One of the first available analyses (not peer-reviewed) of prolonged COVID-19 symptoms was published by the Patient-Led Research Team, a self-organised group of COVID-19 long-haulers conducting research on COVID-19 prolonged recoveries. The report analysed symptoms from 640 people (mostly not hospitalised), half of which (47.8%) were not tested for SARS-

included all respondents in the analysis and found that the main difference between people who tested positive and those testing negative was the timing of the test compared to illness onset. The report identified 'brain fog' and concentration challenges as symptoms more common than cough during most weeks. This result was also confirmed by a survey published in July by Survivor Corps, a US-based patient group. The Patient-Led Research Team is currently working on their second report, focusing on antibody testing, neurological symptoms and mental health in prolonged COVID-19 recoveries. Survivor Corps is now recruiting participants for a follow up survey, focusing on symptom duration and severity.

At the beginning of July, Long COVID SOS, a UK-based advocacy group, started a campaign for recognition of the debilitating effects of long COVID. In July they submitted written evidence to the All Party Parliamentary Group on Coronavirus, a cross-party group conducting an inquiry on the Government response to the pandemic. In August, Long COVID SOS presented oral evidence to the APPG on Coronavirus and organised a meeting with the World Health Organization together with other patient groups.

COVID-19 as a multisystem disease: long-term health effects in different systems

COVID-19 is a disease affecting multiple systems, including the respiratory, cardiovascular, renal, nervous, musculoskeletal and metabolic systems. The effects of SARS-CoV-2 infection have also been reported in other organs, including the gastrointestinal tract and the skin.

According to a report published by the British Society for Immunology, SARS-CoV-2 may cause long-term damage to different organs through a variety of mechanisms: 1) direct effects of viral infection and tissue damage; 2) excessive inflammation and subsequent damage; 3) post-viral autoimmunity; and 4) complications emerging from the formation of blood clots.

Effects of COVID-19 on the respiratory system

Evidence on long-term respiratory complications following COVID-19 is still emerging. A recent commentary highlighted that lung fibrosis (when lung tissue becomes scarred) is seen in mild, moderate and

severe acute respiratory syndrome (SARS) and influenza highlight that impairments in lung function can last for years. The NHS guidance on 'Aftercare needs of inpatients recovering from COVID-19' identifies the following as potential long-term respiratory issues: chronic cough, lung fibrosis, bronchiectasis (widening of the airways) and lung cancer. This is in line with the British Thoracic Society guidance on respiratory follow-up of COVID-19 patients.

Effects of COVID-19 on the cardiovascular system

SARS-CoV-2 infects cells by attaching to the angiotensin-converting enzyme 2 (ACE-2) receptors located on the cells' surface. ACE-2 is not only present in the lungs, but also in blood vessel cells and the heart. ACE-2 receptors have a role in heart function, hypertension and diabetes.

Previous data from patients suffering from diseases caused by similar coronaviruses, such as SARS and Middle Eastern respiratory syndrome (MERS), showed several heart complications in these patients, such as low blood pressure, irregular heart rhythm, heart attacks and heart failure.

SARS-CoV-2 and the vascular system

There is emerging evidence on the effects of COVID-19 on the cardiovascular system and reviews on cardiovascular manifestations and emerging therapeutics are increasing. A recent review on the clinical data available on COVID-19 and the cardiovascular system highlighted that vascular complications are common in COVID-19 patients. For example, formation of blood clots (thrombosis) is seen in 31% of COVID-19 patients in intensive care units. The British Thoracic Society published guidance on this complication in COVID-19 patients.

SARS-CoV-2 can infect the cells that are part of blood vessels of different sizes, such as the coronary artery, which supplies blood to the heart, or smaller vessels branching from it. This could lead to acute coronary syndrome, a group of symptoms including heart attacks that follow decreased blood flow to the heart.

Scientists hypothesise that the observed effects on the vascular system are caused by the interaction between SARS-CoV-2 and the ACE-2 receptor. During infection, levels of ACE-2 decrease and its role in maintaining normal blood pressure is impaired. Others hypothesise

SARS-CoV-2 and the heart

SARS-CoV-2 is able to infect heart tissue; an autopsy from 39 patients who died from COVID-19 found evidence of SARS-CoV-2 in the heart of 24 of them (61.5% of the total). 16 of these patients showed higher virus quantities, but little evidence of an inflammatory response to the virus.

According to NICE guidance, heart complications in COVID-19 patients occur in 1 in 10 patients. These include heart attack, heart failure, irregular or abnormal heart rhythm, and heart inflammation. Heart complications have also been reported anecdotally in a 53-year old patient with no respiratory symptoms. An Italian group reported heart injury in five children showing severe COVID-19 symptoms who were admitted into a paediatric intensive care unit.

Chronic consequences of COVID-19 on the cardiovascular system

Chronic damage to the cardiovascular system has been reported in patients suffering from conditions similar to COVID-19. A 12-year follow-up of 25 patients who recovered from 2003 SARS-CoV found that 44% of them had cardiovascular system abnormalities. A 10-year follow-up of patients hospitalised for pneumonia found an association between hospitalisation for pneumonia and subsequent risk of cardiovascular disease.

Long-term studies on COVID-19 in the cardiovascular system are increasing. A recent study on 100 patients that had recovered from COVID-19 performed heart magnetic resonance imaging (MRI) more than 2 months after they have tested positive for SARS-CoV-2. Almost 1 in 5 reported atypical chest pain and palpitations at the time of the MRI. 78% of the patients had an abnormal MRI scan, and 60% had inflammation and scarring in their heart tissue. Experts urged for more data to be collected to confirm the long-term effects of SARS-CoV-2 in the cardiovascular system. Importantly, some COVID-19 therapies under investigation have important side effects on the cardiovascular system and may worsen the effects of SARS-CoV-2. Their long-term effects are still unknown.

Effects of COVID-19 on the renal system

Acute kidney injury (AKI) is sudden damage to the kidneys that is a common complication in 40% of hospitalised COVID-19 patients. An

kidney function are still under investigation, a study found that only 42% of AKI patients with COVID-19 recovered baseline kidney function compared with 70% of those who had AKI in the absence of COVID-19.

Effects of COVID-19 on the nervous system

There is increasing evidence for the effects of SARS-CoV-2 on the nervous system, which can occur in almost 20% of COVID-19 cases. Neurological complications have been reported in cases of 2003 SARS-CoV, with the virus being detected in brain tissue during autopsy. To date, one report found the genetic material of SARS-CoV-2 in the fluid surrounding the brain and the spinal cord, but not in the airways, where SARS-CoV-2 is commonly detected. A recent report (not peer-reviewed) found ACE-2 receptors in the brain, suggesting that SARS-CoV-2 could invade the organ using its established receptor.

Acute effects on the nervous system

According to a recent review, there are several neurological symptoms of COVID-19, such as the common loss of smell and taste (also present in the absence of other symptoms) or headache. Encephalitis (brain inflammation), Guillain–Barré syndrome (a condition that affects the nerves and causes muscular weakness), and stroke (seen in 2–6% of patients hospitalised with COVID-19) have also been reported. Seizures and impaired consciousness are other, rarer, neurological symptoms of COVID-19. The effects of SARS-CoV-2 on the nervous system can be explained by four mechanisms that can work in combination: 1) direct viral infection, 2) systemic inflammation, 3) dysfunction of organs such as kidneys or lungs, and 4) changes in the cardiovascular system (see above).

Chronic effects on the nervous system

A systematic review analysing data from SARS and MERS found that patients experienced chronic symptoms including depression, insomnia, anxiety, irritability, memory impairment, fatigue, traumatic memories and sleep disorder.

According to a 4-year follow-up study, almost a third of SARS patient reported post-infection fatigue that resulted in a diagnosis of Chronic Fatigue Syndrome (CSF). CFS is a long-term illness with several symptoms, including extreme tiredness; sleep problems; muscle or joint pain; headaches; problems in thinking, remembering or

does not appear to be an association between COVID-19 and CFS.

Due to the widespread inflammation triggered by SARS-CoV-2 infection, scientists hypothesise that COVID-19 patients may be at higher risk of developing cognitive decline. While continued reporting on cases allows scientists to better identify acute COVID-19 symptoms, including the rarest complications, longitudinal studies are needed to understand the long-term consequences of COVID-19 on the nervous system.

Currently, as part of the aftercare needs of inpatients recovering from COVID-19, the NHS indicates monitoring fatigue, delirium, cognitive difficulties and mental health problems.

Emerging effects of COVID-19 on the musculoskeletal system

Evidence from 2003 SARS could shed light on other long-term effects of COVID-19. For instance, the long-term consequences of COVID-19 on muscles and bones are still unknown, but there is increasing evidence that muscle and joint pain are common COVID-19 symptoms. Patients who suffered from moderate or severe SARS reported muscle aches, muscle dysfunction, osteoporosis and osteonecrosis (a disease due to reduced blood flow to bones in the joints) as common long-term consequences of infection.

Emerging effects of COVID-19 on the metabolic system

Data from a 12-year follow-up study of SARS patients highlighted the presence of metabolic dysfunctions, suggesting that possible long-term metabolic complications may also be present in COVID-19 patients. New-onset diabetes has been reported in COVID-19 patients and scientists have established a global registry of patients with COVID-19-related diabetes to better understand this phenomenon.

How to best support patients?

Scientists warn that prolonged and periodic COVID-19 symptoms should be taken into account when setting guidelines for self-isolation and return to work. They also argue that addressing functional disabilities arising from long-term effects of COVID-19 should be a healthcare priority. UK-based primary care experts are currently discussing best practices to manage and support recovery from long-

the UK Government and devolved administrations to develop plans to manage the long-term health consequences of COVID-19, including primary care funding.

In a recent report, the British Society for Immunology recommended long-term (5–10 year) cohort studies to be established to investigate long-term disease consequences in COVID-19 patients.

UK-based initiatives

In early July, the UK Government announced £8.4 million to support the post-hospitalisation COVID-19 (PHOSP-COVID) study, a research study into the long-term health impacts of COVID-19 led by the University Hospitals of Leicester NHS Trust. The project will collect data from around 10,000 patients and share resources with other researchers to improve health outcomes in the future. A caveat of the study is that it focuses only on hospitalised patients, while evidence suggests that people experiencing long-term COVID-19 symptoms often had only mild acute symptoms and were therefore not hospitalised.

On 5 July, the NHS announced the launch of 'Your COVID recovery', an online tool to increase access to COVID-19 rehabilitation. Scientists welcomed this initiative but argued that it should incorporate more inputs from individuals who suffer from long COVID symptoms.

On 23 July 2020, the Scientific Advisory Group for Emergencies (SAGE) discussed the direct and indirect impacts of COVID-19 on excess deaths and morbidity. The document analysed the short, medium and long-term health impacts for survivors of COVID-19.

Research and Innovation for post COVID-19 Rehabilitation (RICOVR) is a research and innovation unit based at the Advanced Wellbeing Research Centre (Sheffield Hallam University), currently recruiting participants to study COVID-19 rehabilitation.

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